PATENT
Docket No. 251502007500
Client Reference N.79639A

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Tamara Alcaraz

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Jordi GRACIA FERRER et al.

Application No.: To Be Assigned

Filing Date: Herewith

For: 8-PHENYL-6,9-DIHYDRO-[1,2,4]TRIAZOLO[3,4-*i*]PURIN-5-ONE DERIVATIVES

Examiner: To Be Assigned

Group Art Unit: To Be Assigned

PRELIMINARY AMENDMENT

Box PATENT APPLICATION
Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Prior to examination of the above-captioned application, please enter the following amendments.

AMENDMENTS

In the Specification:

Please insert the following on page 1, below the title

Cross Reference to Related Applications

This application claims priority from Spain application no. 9901694 filed July 27, 1999 and PCT application no. PCT/EP00/07062 filed July 24, 2000, the contents of each are incorporated herein by reference.

In the Claims:

Please cancel claims 17, 21 and 22

Please amend the following claims

3. (Amended) A compound according to claim 1 wherein R^2 and R^3 independently represent a C_1-C_5 alkyl group, a C_{3-10} cycloalkyl group, or a group of formula

$$-(CH_2)_nR^6$$

wherein n is 0, 1 or 2 and R^6 represents an unsubstituted or substituted phenyl or pyridyl group.

4. (Amended) A compound according to claim 1 wherein R^1 is a methyl, ethyl, propyl, pyridyl, pyridylmethyl, benzyl or *N*-morpholinylmethyl group; R^2 is an ethyl, propyl, n-butyl, i-butyl, n-pentyl, methoxyethyl, substituted or unsubstituted benzyl or 3-pyridylmethyl group; and R^3 is an ethyl, propyl or n-butyl group.

5. (Amended) A compound according to claim 1 wherein the ring formed by R^4, R^5 and the nitrogen atom to which they are attached is a piperidyl, piperazinyl, [1,4]diazepan-1-yl, morpholinyl, pyrazolyl, azetidinyl, diazabicyclo[2.2.1]hept-2-yl or hexahydro-pyrrolo[1,2-a] pyrazinyl group which is unsubstituted or substituted by one or more groups selected from a C_1-C_4 alkyl, C_2-C_4 alkenyl, carbamoyl, amino, di-C_1-C_4-alkylamino, (2- hydroxyethyl)methylamino, hydroxyl, 2,2,2-trifluoroethanoyl, 2,2,2-trifluoroethyl, formyl and hydroxyalkyl groups, alkoxyalkyl groups and hydroxyalkoxyalkyl groups wherein the alkyl moieties contain from 1 to 4 carbon atoms.

7. (Amended) A compound according to claim 1 wherein R^4 and R^5 independently represent hydrogen, a C_1-C_4 alkyl group which is unsubstituted or substituted by a hydroxy or dimethyl amino group, a propynyl group or an amidino group.

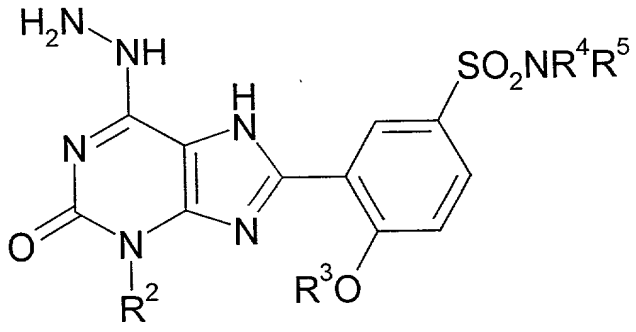
8. (Amended) A compound according to claim 1 wherein R^4 is hydrogen or a C_1-C_4 alkyl group and R^5 represents a group of formula

$$-(CH_2)_nR^7$$

wherein n is 0, 1, 2 or 3 and R^7 is a pyridyl, piperidyl, piperazinyl, morpholinyl, triazolyl, tetrazolyl, pyrrolidinyl, 1-ethylaminocyclohex-1-yl, 1-diethylaminocyclohex-1-yl, 1-ethylaminocyclohept-1-yl, 1-diethylaminocyclohept-1-yl, 3,4-dimethoxyphenyl, 1-methyl-4-phenylpiperidin-4-yl, imidazoyl, 1-methylpiperid-4-yl, tetrahydrofuranyl, 2,2,6,6,-tetramethylpiperid-4-yl, 4-hydroxypiperid-4-yl, 1-acetamidocyclohept-1-yl, 1-methyl-3-azetidinyl or 4-methylpiperazin-1-yl group.

9. (Amended) A compound according to claim 1 characterised in that it has an IC_{50} value for the inhibition of PDE 5 of less than 30 nM.

11. (Amended) A process for preparing a compound as defined in claim 1 which process comprises reacting a
hydrazinopurine derivative of formula (II)



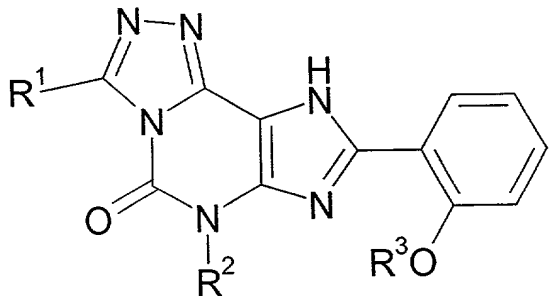
(II)

wherein R^2, R^3, R^4 and R^5 are as defined in claim 1, with a carboxylic acid of the general formula (III):

(III) $R^1—CO_2H$

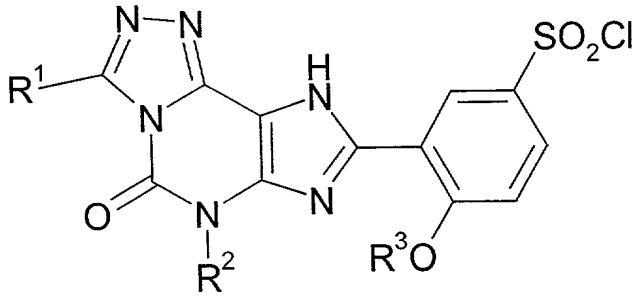
wherein R^1 is as defined in claim 1, or a reactive derivative thereof optionally in the presence of a polar aprotic solvent.

18. (Amended) A process for preparing a compound as defined in claim 1 which process comprises reacting a phenylxanthine of formula (IX):



(IX)

wherein R^1, R^2 and R^3 are as defined in claim 1, with chlorosulphonic acid so as to obtain the sulphonyl chloride of formula (X):



(X)

wherein R^1, R^2 and R^3 are as defined in claim 1, and reacting the sulphonyl chloride of formula (X) with an amine of formula (VIII):

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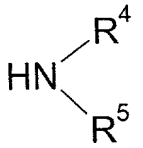


(VIII)

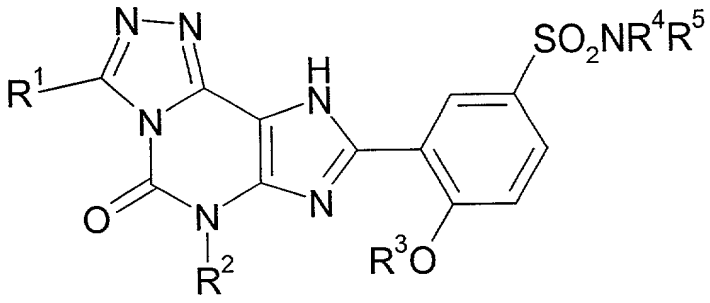
wherein R^4 and R^5 are as defined in claim 1.

20. (Amended) A pharmaceutical composition comprising as an active ingredient, at least one compound as defined in claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In the Abstract:

Please replace the abstract with the following

8-phenyl-6,9-dihydro-[1,2,4]triazolo[3,4-*i*]purin-5-one derivatives of formula (I):



(I)

or a pharmaceutically acceptable salt thereof; process for their preparation, pharmaceutical compositions containing them and their use as PDE 5 inhibitors.

REMARKS

Claims 17, 21 and 22 have been cancelled. Claims 3, 4, 5, 7, 8, 9, 11, 18 and 20 have been amended. These amendments are not intended to abandon, disclaim or dedicate any subject matter.

The amendments to the specification has been made to make of record any cross reference. The abstract has also been amended. Accordingly, Applicants submit no new matter by these amendments.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made**".

In the unlikely event that the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 251502007500. **PLEASE DO NOT CHARGE THE FILING FEES. APPLICANTS WILL PAY FILING FEES WITH RESPONSE TO NOTICE TO FILE MISSING PARTS.**

Respectfully submitted,

Dated: January 25, 2002

By: Gladys H. Monroy

Gladys H. Monroy
Registration No. 32,430

Morrison & Foerster LLP
755 Page Mill Road
Palo Alto, California 94304-1018
Telephone: (650) 813-5711
Facsimile: (650) 494-0792

Version with markings to show changes made

In the Claims:

Please amend the following claims

3. (Amended) A compound according to claim 1 [or claim 2]wherein R^2 and R^3 independently represent a C_1-C_5 alkyl group, a C_{3-10} cycloalkyl group, or a group of formula

$$-(CH_2)_nR^6$$

wherein n is 0, 1 or 2 and R^6 represents an unsubstituted or substituted phenyl or pyridyl group.

4. (Amended) A compound according to [any one of]claim[s] 1[to 3] wherein R^1 is a methyl, ethyl, propyl, pyridyl, pyridylmethyl, benzyl or *N*-morpholinylmethyl group; R^2 is an ethyl, propyl, n-butyl, i-butyl, n-pentyl, methoxyethyl, substituted or unsubstituted benzyl or 3-pyridylmethyl group; and R^3 is an ethyl, propyl or n-butyl group.

5. (Amended) A compound according to [any one of]claim[s] 1[to 4] wherein the ring formed by R^4, R^5 and the nitrogen atom to which they are attached is a piperidyl, piperazinyl, [1,4]diazepan-1-yl, morpholinyl, pyrazolyl, azetidinyl, diazabicyclo[2.2.1]hept-2-yl or hexahydro-pyrrolo[1,2-a] pyrazinyl group which is unsubstituted or substituted by one or more groups selected from a C_1-C_4 alkyl, C_2-C_4 alkenyl, carbamoyl, amino, di-C_1-C_4-alkylamino, (2-hydroxyethyl)methylamino, hydroxyl, 2,2,2-trifluoroethanoyl, 2,2,2-trifluoroethyl, formyl and hydroxyalkyl groups, alkoxyalkyl groups and hydroxyalkoxyalkyl groups wherein the alkyl moieties contain from 1 to 4 carbon atoms.

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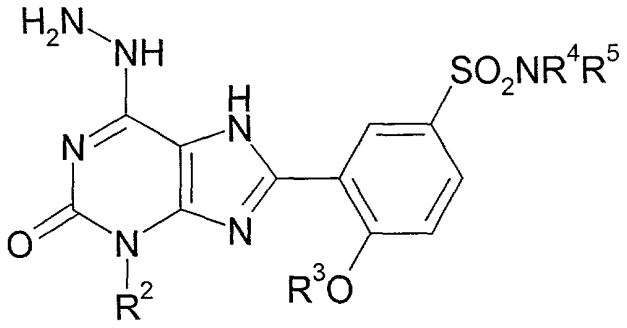
$$-(CH_2)_nR^7$$

wherein n is 0, 1, 2 or 3 and R^7 is a pyridyl, piperidyl, piperazinyl, morpholinyl, triazolyl, tetrazolyl, pyrrolidinyl, 1-ethylaminocyclohex-1-yl, 1-diethylaminocyclohex-1-yl, 1-ethylaminocyclohept-1-yl, 1-diethylaminocyclohept-1-yl, 3,4-dimethoxyphenyl, 1-methyl-4-phenylpiperidin-4-yl, imidazoyl, 1-methylpiperid-4-yl, tetrahydrofuranyl, 2,2,6,6,-tetramethylpiperid-4-yl, 4-hydroxypiperid-4-yl, 1-acetamidocyclohept-1-yl, 1-methyl-3-azetidinyl or 4-methylpiperazin-1-yl group.

9. (Amended) A compound according to [any one of]claim[s] 1[to 8] characterised in that it has an IC_{50} value for the inhibition of PDE 5 of less than 30 nM.

11. (Amended) A process for preparing a compound as defined in [any one of]claim[s] 1[to 10] which process comprises reacting a hydrazinopurine derivative of formula (II)



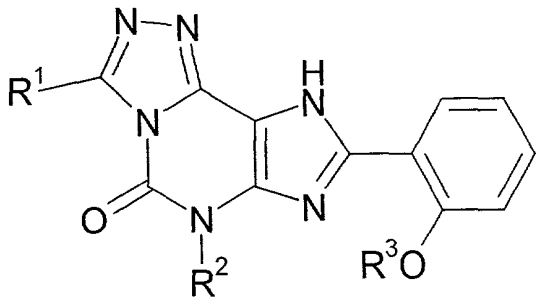
(II)

wherein R^2, R^3, R^4 and R^5 are as defined in [any one of]claim[s] 1[to 10], with a carboxylic acid of the general formula (III):

(III) $R^1—CO_2H$

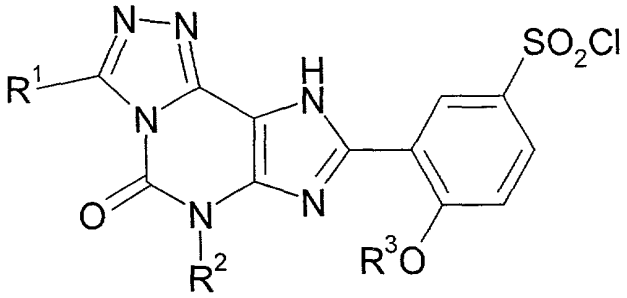
wherein R^1 is as defined in [any one of]claim[s] 1[to 10], or a reactive derivative thereof optionally in the presence of a polar aprotic solvent.

18. (Amended) A process for preparing a compound as defined in [any one of]claim[s] 1[to 10] which process comprises reacting a phenylxanthine of formula (IX):



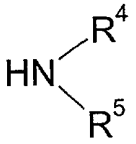
(IX)

wherein R^1, R^2 and R^3 are as defined in [any one of]claim[s] 1[to 10], with chlorosulphonic acid so as to obtain the sulphonyl chloride of formula (X):



(X)

wherein R^1, R^2 and R^3 are as defined in [any one of]claim[s] 1[to 10], and reacting the sulphonyl chloride of formula (X) with an amine of formula (VIII):



(VIII)

wherein R^4 and R^5 are as defined in [any one of]claim[s] 1[to 10].

20. (Amended) A pharmaceutical composition comprising as an active ingredient, at least one compound as defined in [any one of]claim[s] 1[to 10] or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.